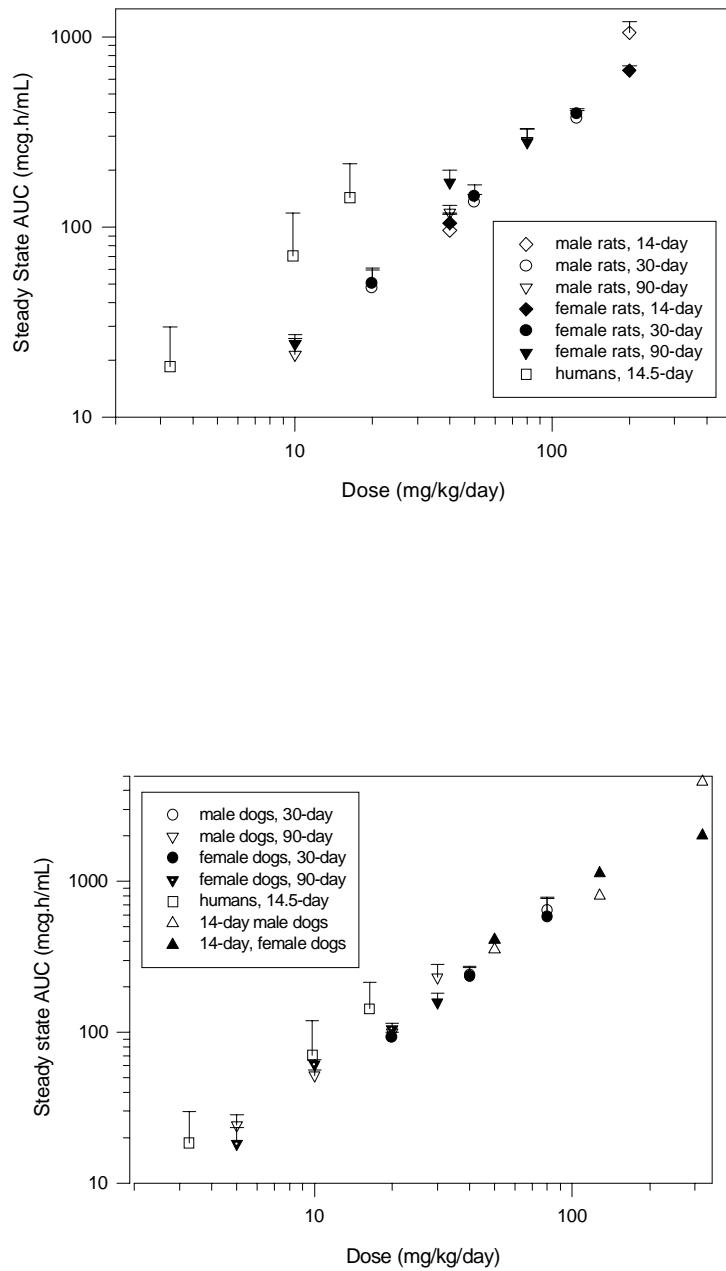
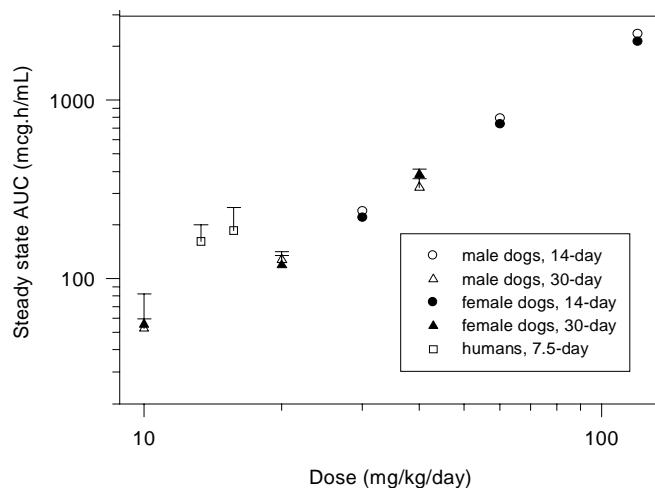
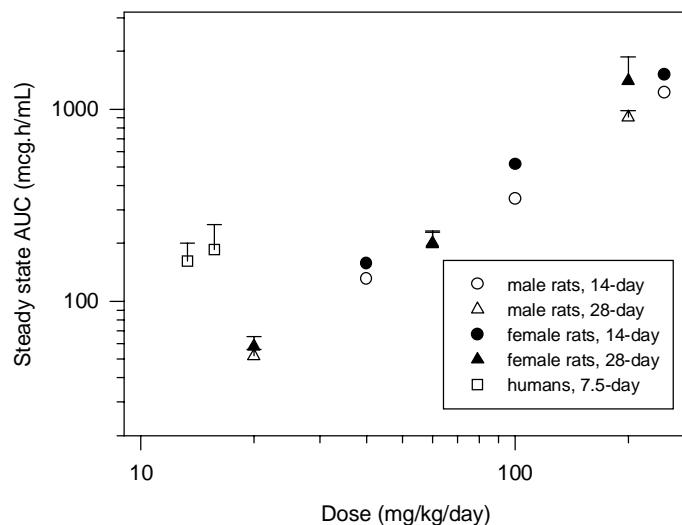


## 5 FIGURES AND TABLES

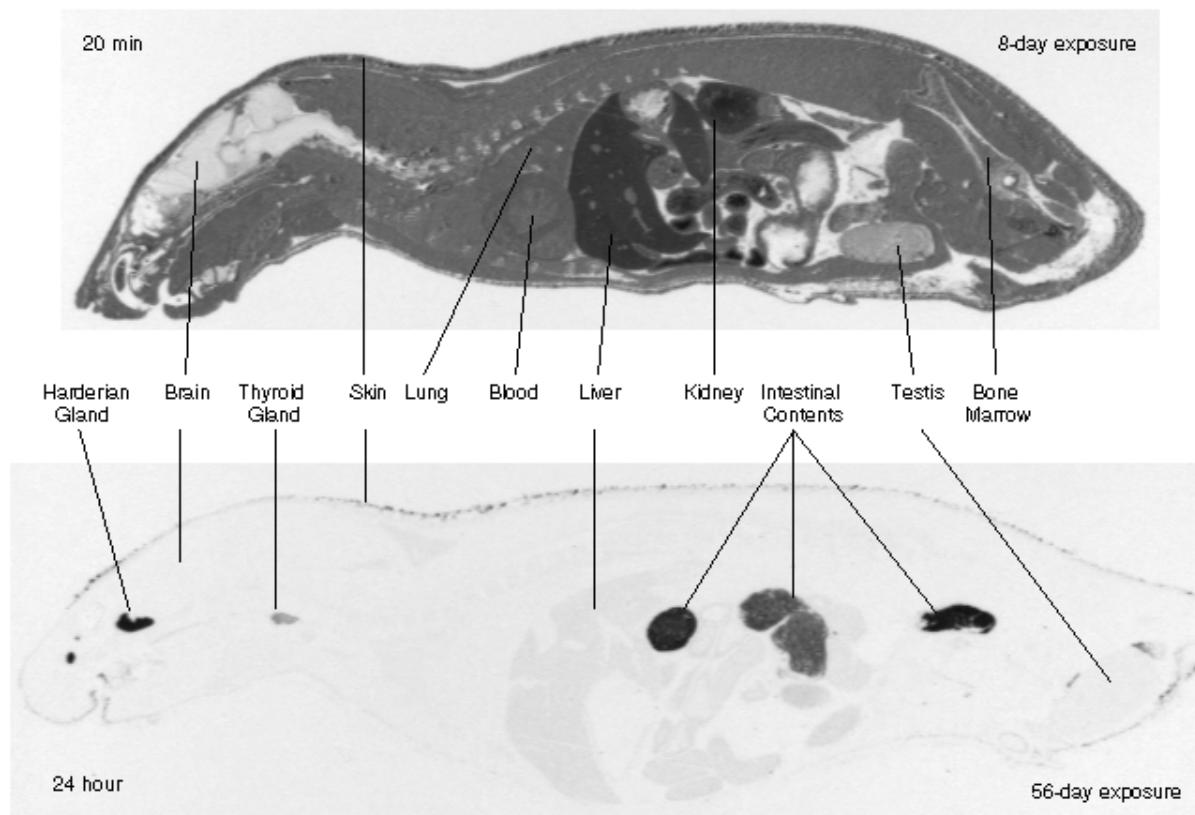
**Figure 1. Steady state AUC of linezolid after oral dose administration to rats (top panel) and dogs (lower panel) in chronic toxicology studies. Data from 2-week dosing of linezolid in humans is included for comparison.**



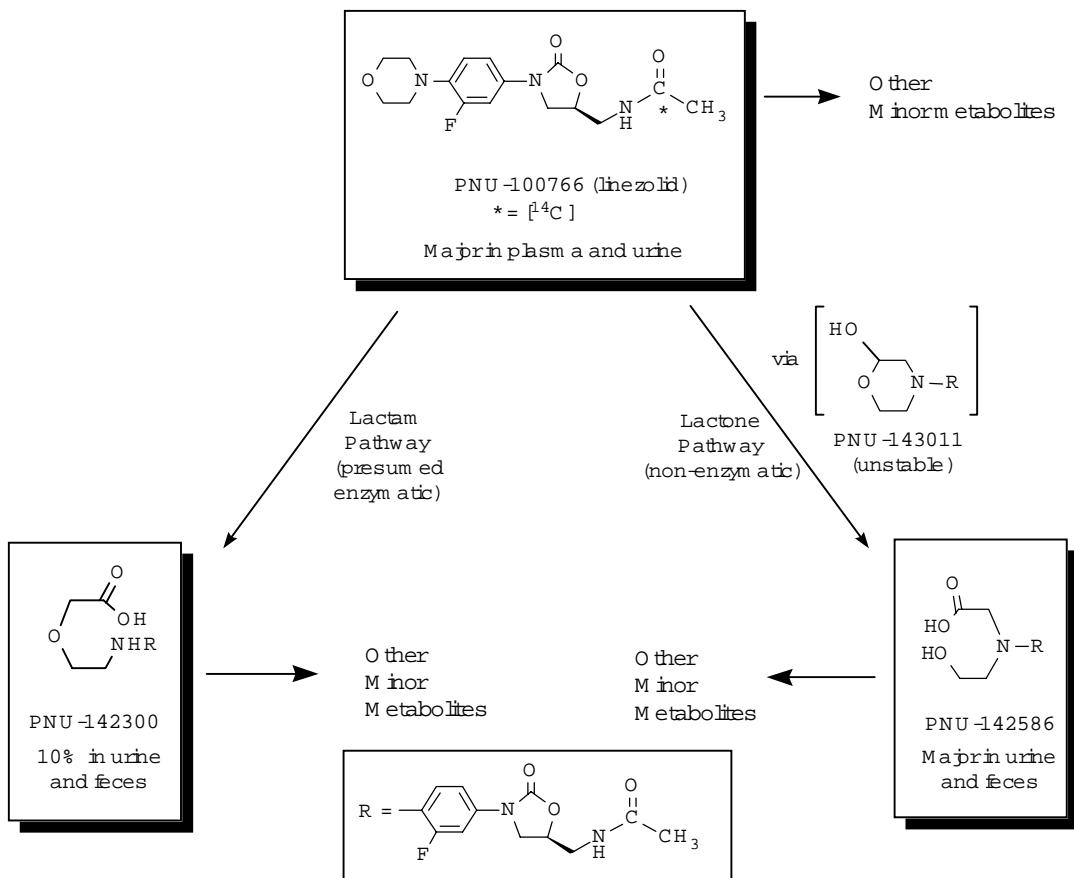
**Figure 2. Steady state AUC of linezolid after intravenous dose administration to rats (top panel) and dogs (lower panel) in chronic toxicology studies. Data from 1-week dosing of linezolid in humans is included for comparison.**



**Figure 3. Images of representative autoradiograms from male Sprague-Dawley rats taken at 20 min and 24 h following single intravenous administration of [<sup>14</sup>C]linezolid at 10 mg/kg. Image darkness is proportional to radioactivity content. Excellent penetration of most soft tissues was observed for this antibiotic compound.**



**Figure 4. Metabolic Pathways for Linezolid in Mouse, Rat, Dog, and Human**



**Table 1. Selected Pharmacokinetic Parameters of Linezolid in Mouse, Rat, and Dog**

Species (Strain)	Route		Dose Level (mg/kg)	Mean Values of Parameters‡							Route of Elimination*
				tmax (h)	Cmax ( $\mu$ g/mL) ( $\mu$ g-eq/g)*	AUC ( $\mu$ g·h/mL)	t1/2 (h)	Vss (L/kg)	CL (mL/min/kg)	F (%)	
Mouse (CH1-HSD)	IV††	3/time point female	4 mg/kg	-	10.5 ± 1.6†	2.2	0.3	0.45	30.2	100	-
			8 mg/kg	-	22.0 ± 4.5†	5.7	0.4	0.64	23.2	100	-
			12 mg/kg	-	41.9 ± 1.5†	14.2	0.5	0.49	14	100	-
	PO	3/time point female	4 mg/kg	0.2	1.7 ± 0.2	1.9	0.5	-	-	86	-
			8 mg/kg	0.2	6.0 ± 1.3	7.1	0.5	-	-	124	-
			12 mg/kg	0.3	11.4 ± 0.9	23.5	1.1	-	-	165	-
Mouse (CD-1)	PO	4 female	50 mg/kg	1	24.0 ± 2.3*	-	-	-	-	-	Urine, 53.1 ± 7.7%* Feces, 32.4 ± 5.0% Total, 92.5 ± 4.0% $^{14}\text{CO}_2$ 4.1% (N=2) (48 h)
Rat (Sprague-Dawley)	IV	3 male	10 mg/kg	-	15.0 ± 0.8†	15.5 ± 1.6	1.0 ± 0.1	0.72 ± 0.02	10.5 ± 1.1	100	-
	PO	3 male	25 mg/kg	0.3 ± 0.2	15.8 ± 3.3	42.6 ± 6.6	1.1 ± 0.3	-	-	109	-
Rat (Sprague-Dawley)	PO	4 male	25 mg/kg	-	-	-	-	-	-	-	Urine, 74.4 ± 2.0%* Feces, 23.6 ± 1.1%* Carcass, 0.6 ± 0.1%* $^{14}\text{CO}_2$ , 2.7%* (n=2) (120 h)

- Not determined

\* Radioactivity

† Concentration in first sample (2 min postdose)

††  $\beta$ -Hydroxypropylcyclodextrin vehicle

‡ Some data rounded to facilitate comparison across studies

**Table 1. Selected Pharmacokinetic Parameters of Linezolid in Mouse, Rat, and Dog  
(continued)**

Species (Strain)	Route	N Sex	Dose Level (mg/kg)	Mean Values of Parameters							Route of Elimination* Mean % of
				tmax (h)	Cmax ( $\mu$ g/mL) ( $\mu$ g·eq/g)*	AUC ( $\mu$ g·h/mL)	t1/2 (h)	Vss (L/kg)	CL (mL/min/kg)	F (%)	
Dog (Beagle)	IV	3 male	25 mg/kg	-	29.6 ± 3.6†	214 ± 37	3.9 ± 0.4	0.63 ± 0.05	2.0 ± 0.3	100	-
		3 male	25 mg/kg capsule	1.0 ± 0.5	26.8 ± 1.5	206 ± 19	3.6 ± 0.1	-	-	96.6 ± 20.7	-
		3 male	25 mg/kg solution	0.8 ± 0.2	28.2 ± 4.1	206 ± 51	3.6 ± 0.4	-	-	97.3 ± 24.3	-
Dog (Beagle)	PO	3 male	25 mg/kg	=	=	=	=	-	-	-	Urine, 50.9 ± 4.9%* (0-168 h)
				=	=	=	=	-	-	-	Feces, 46.4 ± 4.8%* (0-168 h)

- Not determined.

= Not reported (data presented in Table 2)

\* Radioactivity

† Concentration in first sample at 0.8 h postdose

**Table 2. Exposure (AUC Values) at LOAEls and NOAEls in the Pivotal Animal Toxicology Studies Compared with Estimated Human Exposures**

Study	NOAEL/LOAEL (mg/kg/day)	AUC (0-24 h) at NOAEL ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	AUC (0-24 h) at LOAEL ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	Human AUC (0-24 h) ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )*
1-Month Oral Rat	20: NOAEL 50: mild bone marrow effects	49	140	150/275†
1-Month Juvenile Rat	25: NOAEL 63: mild clinical chemistry changes, hair loss	144 (Day 1) 48 (Day 2)	460 (Day 1) 128 (Day 2)	150/275
1-Month Oral Dog	20: NOAEL 40: mild bone marrow hypocellularity	93	236	150/275
3-Month Rat	10: NOAEL 40: minimal reversible effects, including ↓ RBC (m); ↑ MCH (m); ↑ MCV (m); epididymal epithelial cell hypertrophy	23	195	150/275
3-Month Dog	20: NOAEL 30: inappetence/anorexia, ↓ RBC, HCT, HGB, RTC	102	195	150/275
Fertility-Adult Rat‡	15: NOAEL 50: decreased male fertility	67§	222§	150/275
Fertility-Juvenile rat	25/50: NOAEL 50/100: decreased male rat fertility (50 on days 1-36; 100 on days 37-55)	126 (Day 1) 52 (Day 36) 125 (Day 43)	324 (Day 1) 112 (Day 36) 296 (Day 43)	242§
Embryo-Fetal Development Mouse	150: NOAEL 450: maternal toxicity, effects on embryo and fetus	287	1150	150/275
Embryo-Fetal Development Rat	2.5: NOAEL 15: decreased fetal body weights and delayed skeletal ossification	3.3	38	242
Peri-Postnatal Development Rat	15: NOAEL 50: decreased postnatal pup survival and developmental delays	38	176	242

\* Human exposure at 800 and 1200 mg/day for soft skin infections and other indications, respectively

† 150 and 275 are AUCs for adults given doses of 800 and 1200 mg/day, respectively

‡ AUC values were estimated from reference 24. Males given 100 mg/kg/day had mean AUC (0-24) = 444; assuming linear kinetics, AUC at 15 mg/kg/day ≈ 67  $\mu\text{g}\cdot\text{h}/\text{mL}$  and AUC at 50 mg/kg/day ≈ 222.

§ Data from pediatric study M/1260/0028. Mean AUC for 600 mg given IV twice daily was extrapolated from the mean AUC for a single 600 mg IV dose of 121  $\mu\text{g}\cdot\text{h}/\text{mL}$ .

**Abbreviations:** AUC = area under the concentration-time curve; HCT = hematocrit; HGB = hemoglobin; LOAEL = lowest-observed-adverse-effect level; m = males; MCH = mean cell hemoglobin; MCV = mean cell volume; NOAEL = no-observed-adverse-effect level; RBC = red blood cell count; RTC = reticulocyte count;  
↓ = decrease; ↑ = increase.

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
<b>SAFETY PHARMACOLOGY STUDIES</b>					
Cardio-Pulmonary Profile, Anesthetized Dog (Beagle)	IV	0 (vehicle), 3, 10, 30 mg/kg	Sequential, single dose	(A1)1510-5014-TJF-170A-J255	No
Anticonvulsant and Analgesic Activities and Effects on Thiopental-Induced Hypnosis, Rat (Crj:CD[SD])	Anti-convulsant Activity IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	Yes
	Analgesic Activity IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose		
	Thiopental-Induced Hypnosis IV	<u>Main Study:</u> 0 (vehicle), 6, 30, 125 mg/kg <u>Additional Study:</u> 0 (vehicle), 6, 15, 30 mg/kg	Single dose		
Gastrointestinal Profile, Guinea Pig (Hartley)	Isolated Guinea Pig Ileum Test In vitro	$10^{-4}$ , $3 \times 10^{-4}$ M	Single dose	(A1)1510-5014-TJF-170A-J255	No
Gastrointestinal Profile, Rat (Crj:CD[SD])	Gastric Secretion Test PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
	Gastric Emptying Test PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose		
	Intestinal Fluid Volume Test PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose		

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Gastrointestinal Profile, Rat (Crj:CD[SD])	Gastric Secretion Test IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	Yes
	Gastric Emptying Test IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose		
Gastrointestinal Propulsion, Rat (Crl:CD[SD]BR)	IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
Renal Profile, Rat (Crj:CD[SD])	IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	Yes
Functional Observational Battery, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose	(A1)1510-5014-TJF-170A	No
Functional Observational Battery, Rat (Crl:CD[SD]BR)	IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
<b>TOXICOLOGY STUDIES</b>					
<b>Single-Dose Toxicity Studies</b>					
Acute Toxicity, Rat (Crj:CD[SD])	PO	0 (vehicle), 1000, 3000, 5000 mg/kg/day (0, 500, 1500, 2500 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Acute Comparative Toxicity, Rat (CD[SD]BR)	IV	0 (vehicle), 75 (THS), 75 (NH), 150 (THS), 150 (NH) mg/kg	Single dose	(C)5014-TJF-490A	No
Acute Toxicity, Rat (Crj:CD[SD])	IV	0 (vehicle), 100, 200, 400 mg/kg/day (0, 50, 100, 200 mg/kg/dose)	Divided dose (6 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Acute Toxicity, Dog (Beagle)	PO	500, 1000, 2000 mg/kg/day (250, 500, 1000 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	Yes
<b>Repeated-Dose Toxicity Studies</b>					
Comparative Toxicity, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 200 mg/kg/day of either PNU-100766 or PNU-96403*	Twice daily; 7 days	(D2)1500-5148-JLH-48M	No
Range-Finding Toxicity, Rat (Crj:CD[SD])	PO	0 (vehicle), 40, 200, 1000 mg/kg/day (0, 20, 100, 500 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Range-Finding Toxicity, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 100 mg/kg/day (0, 50 mg/kg/dose)	Twice daily; 1 month	27080-DAV-101A	No
Toxicity with Recovery, Rat (Crj:CD[SD])	PO	0 (vehicle), 20, 50, 125 mg/kg/day (0, 10, 25, 62.5 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Toxicity with Recovery, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 10, 40, 125/80 mg/kg/day (0, 5, 62.5/40 mg/kg/dose)	Twice daily; 3 months Recovery: 1 month	(D)5014-TJF-864	Yes
Range-Finding Toxicity, Male Juvenile Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 12.5, 25, 50, 100 mg/kg/day	Daily; 4 weeks	(D)5014-TJF-904	No
Toxicity with Recovery, Juvenile Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 10, 25, 63 mg/kg/day	Daily; 1 month Recovery: 6 weeks	(D)5014-TJF-864	Yes
Toxicity, Juvenile Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 100 mg/kg/day	Daily; 53 days	(D)5014-TJF-864	No
Toxicity, Rat (Crj:CD[SD])	IV	0 (vehicle and environmental [saline] controls), 40, 100, 250 mg/kg/day (0, 0, 20, 50, 125 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity with Recovery, Rat (Crj:CD[SD])	IV	0 (vehicle), 20, 60, 200 mg/kg/day (0, 10, 30, 100 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes
Range-Finding Toxicity, Male Rabbit (NZW)	PO	0 (vehicle), 25, 50, 100 mg/kg/day (0, 12.5, 25, 50 mg/kg/dose)	Twice daily; 7 days	(D)5014-TJF-904	No
Range-Finding Toxicity, Dog (Beagle)	PO	0 (control), 50, 128, 320 mg/kg/day (0, 25, 64, 160 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity with Recovery, Dog (Beagle)	PO	0 (control), 20, 40, 80 mg/kg/day (0, 10, 20, 40 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(A1)1510-5014-TJF-170A-J255	Yes
Toxicity with Recovery, Dog (Beagle)	PO	0 (vehicle), 5, 10, 20, 40/30 mg/kg/day (0, 2.5, 5, 10, 20/15 mg/kg/dose)	Twice daily; 3 months Recovery: 2 months	(D)5014-TJF-864	Yes
Toxicity, Dog (Beagle)†	IV	60, 150 mg/kg/day (30, 75 mg/kg/dose)	Twice daily; 5 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity, Dog (Beagle)	IV	0 (vehicle), 30, 60, 120 mg/kg/day (0, 15, 30, 60 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity with Recovery, Dog (Beagle)	IV	0 (vehicle), 10, 20, 40 mg/kg/day (0, 5, 10, 20 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(C)5014-TJF-490A	Yes
<b>Reproductive Function Studies</b>					
Fertility with Reversibility, Male Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 50, 100 mg/kg/day	Males: daily; 9 weeks Females: untreated Reversibility: up to 12 weeks	(D)5014-TJF-904	Yes
Toxicity and Fertility, Male Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 100 mg/kg/day	Males: daily; 10 weeks Females: untreated Reversibility: up to 14 weeks	(D)5014-TJF-864	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Toxicity and Fertility with Testosterone Supplementation, Male Rat (Crl:CD[SD]BR)	PO	100 mg/kg/day with placebo or testosterone implant	Daily; 10 weeks	(D)5014-TJF-904	No
Toxicity and Fertility with Reversibility, Juvenile Male Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 12.5/25, 25/50, 50/100 mg/kg/day (0, 12.5, 25, 50 mg/kg/day on days 1-36 followed by a dose escalation to 0, 25, 50, 100 mg/kg/day, respectively, on days 37-49.	Daily; 7 weeks Reversibility: up to 19 weeks	(D)5014-TJF-864	Yes
<b>Embryo-Fetal and Perinatal Toxicity Studies</b>					
Preliminary Reproduction, Mouse (Crl:CD-1 [ICR] BR)	PO	0 (vehicle), 5, 25, 75, 150 mg/kg/day	Daily; Gestation days 6-16	(C)5014-TJF-490A	Yes
Supplementary Preliminary Reproduction, Mouse (Crl:CD-1 [ICR] BR)	PO	0 (vehicle), 450, 1000 mg/kg/day	Daily; Gestation days 6-15	(A1)1510-5014-TJF-170A-J255	No
Developmental Toxicity, Mouse (Crl:CD-1 [ICR] BR)	PO	0 (vehicle), 50, 150, 450 mg/kg/day	Daily; Gestation days 6-16	(C)5014-TJF-490A	Yes
Preliminary Reproduction, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 5, 25, 75, 125 mg/kg/day	Daily; Gestation days 6-21	(A1)1510-5014-TJF-170A-J255	No
Developmental Toxicity, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 2.5, 15, 50 mg/kg/day	Daily; Gestation days 6-19	(C)5014-TJF-490A	Yes
Combined Segment I and III Fertility, General Reproductive Performance, and Postnatal Development, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 2.5, 15, 50 mg/kg/day	Males: Daily; 4 weeks prior to and throughout cohabitation until sacrifice  F0 Females that Delivered: 2 weeks prior to cohabitation throughout cohabitation, gestation, and postpartum until sacrifice at weaning  F0 Supplementary Phase Treated Females: 2 weeks prior to cohabitation until sacrifice on gestation day 13	(C)5014-TJF-490A	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
<b>Mutagenic Potential Studies</b>					
Ames Assay in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i>	In vitro	0 (DMSO), 6.8, 20, 61, 183, 550 µg/plate with and without metabolic activation	2-day incubation	(A1)1510-5014-TJF-170A	Yes
Unscheduled DNA Synthesis (UDS) Assay, Rat Primary Hepatocytes	In vitro	0, 3, 10, 30, 100, 300, 600, 1000, 2000 µg/mL	18-20 hour incubation	(A1)1510-5014-TJF-170A	Yes
AS52/XPRT Mammalian Cell Mutation Assay With and Without Metabolic Activation	In vitro	0 (DMSO), 125, 150, 450, 900, 1800, and 3600 µg/mL with metabolic activation, and 0 (solvent, DMSO), 112.5, 225, 450, 900, 1800, and 3600 µg/mL without metabolic activation	18-20 hour incubation	(A1)1510-5014-TJF-170A	Yes
Chromosome Aberration Assay, Human Peripheral Lymphocytes	In vitro	<u>Experiment a1:</u> 0 (McCoy's 5A medium), 500, 1000, 2000 µg/mL without metabolic activation <u>Experiment a2:</u> 0 (McCoy's 5A medium), 250, 500, 1000 µg/mL without metabolic activation <u>Experiment b:</u> 0 (McCoy's 5A medium), 500, 1000, 2000 µg/mL with and without metabolic activation	<u>Experiment a1:</u> 24-hour incubation <u>Experiment a2:</u> 48-hour incubation <u>Experiment b:</u> 3-hour incubation	(A1)1510-5014-TJF-170A	Yes
Micronucleus Test in Bone Marrow Cells, Mouse	PO	0 (vehicle), 1000, 2500, 5000 mg/kg	Single dose	(A1)1510-5014-TJF-170A	Yes
<b>Other Studies</b>					
Handler Safety Studies					
Ocular Irritation, Rabbit (NZW)	Topical	100 mg/eye  20 mg/eye/day	Single dose  Daily; 5 days	(A1)1510-5014-TJF-170A	No
Dermal Irritation, Rabbit (NZW)	Topical (intact and abraded skin sites)	500 mg/site  100 mg/site/day	Single dose  Daily; 5 days	(A1)1510-5014-TJF-170A	No
<b>MAO Inhibition Studies</b>					
NovaScreen Data	In vitro	$10^{-8}$ , $10^{-6}$ , $10^{-1}$ M	60 minutes	NR	No
Monoamine Oxidase Inhibition	In vitro	2, 20, 200 µM	30 minutes	NR	No

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Development of Microtiter Plate-Based Assays for MAO-A and MAO-B	In vitro	NA	NA	NA	No
Cardiovascular and Sympathomimetic Vasopressor Responses, CUP-Anesthetized Rat	IV	0 (vehicle), 5, 15 mg/kg	Single dose	NR	No
Cardiovascular and Sympathomimetic Vasopressor Responses, CUP-Anesthetized Rat	PO	0 (vehicle), 30, 100 mg/kg/day (0, 15, 50 mg/kg/dose)	Divided dose administered twice daily for 3.5 days	(D)5014-TJF-864	No
Cardiovascular and Sympathomimetic Vasopressor Responses, CUP-Anesthetized Rat	PO	0 (vehicle), 30, 90 mg/kg/day (0, 10, 30 mg/kg/dose)	One-third dose administered three times daily for 14.3 days	(D)5014-TJF-904	No
Effects of MAOs, Isoniazid, and Oxazolidinone Antibiotics (PNU-100766, PNU-100592 and PNU-108812) on Vasopressor Response to Oral Tyramine, Conscious Rat (SD)	PO	0 (vehicle), 5, 15, 50 mg/kg/dose	Divided dose, twice daily for 2.5 days	(C)5014-TJF-490A	No
Further Evaluation of Selected MAOs, PNU-100766, and PNU-108812 for Oral Tyramine Potentiation, Male Rat (SD)	PO	<u>Study B:</u> 0 (vehicle), 50 mg/kg/dose <u>Study C:</u> 0 (vehicle), 15, 50, 100 mg/kg <u>Study D:</u> 0 (vehicle, 15, 50 mg/kg	<u>Study B:</u> Divided dose, twice daily for 0.5, 1.5, or 2.5 days (1, 3, or 5 doses) <u>Study C:</u> Single dose <u>Study D:</u> Single dose	(C)5014-TJF-490A	No
Tyramine Potentiation in Conscious Rats Treated with Oxazolidinone Antibiotics, Male Rat (HDS[SD])	PO or IV	50 mg/kg PO 10 mg/kg bolus + 12 mg/kg/hr IV	Single dose Single bolus injection + 2.75 hr infusion	NR	No
Oral Tyramine Potentiation in Conscious Rats Treated with Oxazolidinone Antibiotics, Male Rat (HDS[SD])	PO or IV	50 mg/kg PO 10 mg/kg bolus + 12 mg/kg/hr IV	Single dose Single bolus injection + 1.25 hr infusion	NR	No
Evaluation of Vasopressor Interactions Between PNU-100766 and Five Marketed Cold Remedies, Conscious Male Rat (SD)	PO	5, 15, 50 mg/kg/dose	Divided dose, twice daily for 2.5 days	(C)5014-TJF-490A	No

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Vasopressor Responses to Aqueous Formulations of Phenylpropanolamine, Pseudoephedrine, and Dextromethorphan in Rats Treated with MAOs and PNU-100766, Male Rat (SD)	PO	15, 50 mg/kg	Single dose	(C)5014-TJF-490A	No
Cardiovascular Responses to Tyramine and Decongestant Amines After Treatment with PNU-100766, Conscious Female Dog (Beagle)	PO	<u>Pilot Test:</u> 10 mg/kg (day 2) and 25 mg/kg (day 3) <u>Definitive Study:</u> 0 (control), 20 mg/kg/dose	<u>Pilot Test:</u> Single dose <u>Definitive Study:</u> Twice daily for 3.5 days than crossover 1 week later for 3.5 days	(C)5014-TJF-490A	No
Monoamine Oxidase Inhibition, Male Mouse (CF)	PO	0 (vehicle), 50 mg/kg	Single dose	NR	No
Effects on Rat Brain Monoamine Levels After Acute and Chronic Exposure, Male Rat (SD)	<u>Acute:</u> SC <u>Chronic:</u> PO	<u>Acute Study:</u> 30, 90 mg/kg <u>Chronic Study:</u> 10, 30 mg/kg/dose	<u>Acute Study:</u> 2 hours <u>Chronic Study:</u> TID for 14 days with 0, 2, 5, or 13 days recovery	NR	No
Effects in Rabbit Model of Hyperpyrexia, Rabbit	PO	50, 150 mg/kg/dose	2 doses	NR	No
Serotonin Syndrome, Rabbit (NZW)	PO	50 mg/kg/dose	1 dose 18 hours before surgery and 1 dose the morning of surgery	NR	No
Studies on Impurities and Degradation Products					
Ames Assay in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> with PNU-105368†	In vitro	0 (DMSO), 313, 625, 1250, 2500, 5000 µg/plate with and without metabolic activation	2-day incubation	29419-DAU-107A	Yes
Ames Assay in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> with PNU-141535	In vitro	0 (sterile water), 7, 21, 62, 185, 555 µg/plate with metabolic activation  0 (sterile water), 62, 185, 556, 1667, 5000 µg/plate without metabolic activation	2-day incubation	(A)410-FCW-43	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Unscheduled DNA Synthesis (UDS) Assay with PNU-105368‡, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 50, 100, 200, 300, 500, 750 µg/mL <u>Experiment 2:</u> 50, 100, 200, 300, 500, 750 µg/mL	18-20 hour incubation	29419-DAU-107A	Yes
Unscheduled DNA Synthesis (UDS) Assay with PNU-105368‡, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 3, 10, 30, 100, 300, 1000 µg/mL <u>Experiment 2:</u> 100, 200, 300, 500, 750, 1000 µg/mL	18-20 hour incubation	NR	No
Unscheduled DNA Synthesis (UDS) Assay with PNU-141535§, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 30, 100, 300, 600, 1000, 3000 µg/mL <u>Experiment 2:</u> 30, 60, 200, 600, 2000, 3000 µg/mL	18-20 hour incubation	(A)410-FCW-43	Yes
Unscheduled DNA Synthesis (UDS) Assay with PNU-141535§, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 10, 30, 100, 300, 1000, 3000 µg/mL <u>Experiment 2:</u> 100, 300, 600, 1000, 2000, 3000 µg/mL	18-20 hour incubation	NR	No
Unscheduled DNA Synthesis (UDS) Assay with PNU-105368‡, Rat (Fischer 344)	In vivo (IP) and in vitro	0 (DMSO), 100, 200, 400 mg/kg	Single dose 2 or 16 hours before sacrifice	29419-DAU-107A	Yes
Unscheduled DNA Synthesis (UDS) Assay with PNU-141535§, Rat (Fischer 344)	In vivo (IV) and in vitro	0 (saline), 500, 1000, 2000 mg/kg	Single dose 2 or 16 hours before sacrifice	(A)410-FCW-43	Yes
AS52/XPRT Mammalian Cell Mutation Assay with PNU-105368‡, AS52 Chinese Hamster Cells	In vitro	<u>Experiment 1:</u> 0 (DMSO), 10, 100, 1000, 2000, 4000 µg/mL without metabolic activation 0 (DMSO), 100, 500, 1000, 2500, 5000 µg/mL with metabolic activation <u>Experiment 2:</u> 0 (DMSO), 500, 1000, 2000, 3000, 4000 µg/mL without metabolic activation 0 (DMSO), 500, 1000, 2000, 3000, 4000, 5000 µg/mL with metabolic activation	5-hour incubation	29419-DAU-107A	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
AS52/XPRT Mammalian Cell Mutation Assay with PNU-141535§, AS52 Chinese Hamster Cells	In vitro	<u>Experiment 1:</u> 0 (sterile water), 100, 500, 1000, 2500, 5000 µg/mL with and without metabolic activation <u>Experiment 2:</u> 0 (sterile water), 250, 500, 1000, 2500, 5000 µg/mL with and without metabolic activation	5-hour incubation	(A)410-FCW-43	Yes
Chromosome Aberration Assay in Human Lymphocytes Peripheral with PNU-105368‡	In vitro	0 (solvent), 100, 200, 400 µg/mL without metabolic activation 0 (solvent), 750, 1500, 3000 µg/mL with metabolic activation	24- and 48-hour incubation 3-hour incubation	29419-DAU-107A	Yes
Chromosome Aberration Assay in Human Peripheral Lymphocytes with PNU-141535§	In vitro	0 (solvent), 156.3, 312.5, 625 Tg/mL without metabolic activation 0 (solvent), 1250, 2500, 5000 Tg/mL with metabolic activation	24- and 48-hour incubation 3-hour incubation	(A)410-FCW-43	Yes
Micronucleus Test in Bone Marrow Cells with PNU-105368‡, Mouse	PO	Males: 0 (vehicle), 150, 375, 750 mg/kg Females: 0 (vehicle), 200, 500, 1000 mg/kg	Single dose	29419-DAU-107A	Yes
Micronucleus Test in Bone Marrow Cells with PNU-141535§, Mouse	IV	0 (saline), 400, 1000, 2000 mg/kg	Single dose	(A)410-FCW-43	Yes

**ADME STUDIES**

Methodology					
HPLC Plasma Assay, Mouse	NA	LLOQ = 0.01 µg/mL	NA	Reference standard lot; (C)5014-TJF-490A-J363	NA
HPLC Plasma Assay, Rat, Dog	NA	LLOQ = 0.05 µg/mL	NA	(A1)1510-5014-TJF-170A-J255	NA
HPLC Plasma Assay, Rat, Dog	NA	LLOQ = 0.005µg/mL	NA	(C)5014-TJF-490A-J370	NA
HPLC Plasma Assay, Rat, Dog	NA	LLOQ = 0.01 µg/mL	NA	(A1)1510-5014-TJF-170A-J255	NA
HPLC Plasma Assay Validation Report, Rat	NA	LLOQ = 0.02 µg/mL	NA	(D2)1500-5148-JLH-48	NA
HPLC Plasma Assay, Rabbit	NA	LLOQ = 0.01 µg/mL	NA	(A1)1510-5014-TJF-170A	NA

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Metabolite Syntheses & Activity	NA	PNU-142300E, PNU-142586, PNU-142618, PNU-142620, PNU-143010, PNU-143011, PNU-143131, PNU-144089 [105] PNU-173558: [109] PNU-100440/PNU-105368: Linezolid synthetic intermediates [108] Metabolite antibacterial activity [147]	NA	Various	NA
<sup>14</sup> C Radiolabel Synthesis 1	NA	NA	NA	27983-JPM-40B	NA
<sup>14</sup> C Radiolabel Synthesis 2	NA	NA	NA	27792-EHC-76A¶	NA
<b>Single-Dose Pharmacokinetics/Toxicokinetics</b>					
Bioavailability, Mouse (CH1-HSD)	IV, PO	4, 8, 12 mg/kg	Single dose	(D)5014-TJF-967	No
<sup>14</sup> C Pharmacokinetics-Label Stability-Distribution-Excretion, Female Mouse (CD-1)	PO	50 mg/kg	Single dose	30994-JAE-75A	No
<sup>14</sup> C Pharmacokinetics-Excretion-Distribution, Female Mouse (CD-1)	PO	50, 450 mg/kg	Single dose	PNU-100766, GLP10361, GLP10360 [ <sup>14</sup> C]PNU-100766, 30994-JAE-75A, 74A	Yes
Bioavailability, Male Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	27774-DAU-71-A	No
Renal Pharmacokinetics, Male Rat (Sprague-Dawley)	IV	0.8 mg/mL loading dose, 0.3 mg/mL PNU-100766, infusion	Infusion	(A1)1510-5014-TJF-170-A	No
Renal Pharmacokinetics, Male Rat (Sprague-Dawley)	IV	2.5 mg	Single	(C) 5014-TJF-490A	No
<sup>14</sup> C Pharmacokinetics, Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766: A1(1510)-5014-TJF-170A-J255, [ <sup>14</sup> C]PNU-100766: 37792-EHC-7UA	No
<sup>14</sup> C Excretion-Label Stability, Male Rat (Sprague-Dawley)	PO	25 mg/kg	Single dose	PNU-100766: 27774-DAU-71A, [ <sup>14</sup> C]PNU-100766: 27983-JPM-40B; RA 0231.	No
Pharmacokinetics/ Hydroxypropylcyclodextrin Vehicle Effect, Rat (Sprague-Dawley)	IV	5 mg/kg	Single dose	(C) 5014-TJF-490A	No

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 1000, 3000, 5000 mg/kg/day (0, 500, 1500, 2500 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Toxicokinetics, Rat (Sprague-Dawley)	IV	0 (vehicle), 100, 200, 400 mg/kg/day (0, 50, 100, 200 mg/kg/dose)	Divided dose (6 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Bioavailability, Male Dog (Beagle)	PO, IV	25 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
Toxicokinetics, Male Dog (Beagle)	PO	500, 1000, 2000 mg/kg/day (250, 500, 1000 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
<sup>14</sup> C Pharmacokinetics-Excretion, Male Dog (Beagle)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	(A1)1510-5014-TJF-170A-J255, [ <sup>14</sup> C]PNU-100766: 37792-EHC-7UA	No
<sup>14</sup> C Pharmacokinetics-Excretion, Female Dog (Beagle)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	[ <sup>14</sup> C] 30484-JAE-47A & 5014-TJF-864	Yes
Studies On Metabolite PNU-105368					
PNU-105368 Metabolite Toxicokinetics, Mouse (CD-1)	PO	50, 500, 2000 mg/kg (range finding) 150, 375, 750 mg/kg (definitive)	Single dose	29419-DAU-107A	No
PNU-105368 Metabolite Toxicokinetics, Rat (Fischer 344)	IP	100, 200, 400 mg/kg	Single dose	29419-DAU-107A	No
Studies On Process Impurity PNU-141535					
PNU-141535 Process Impurity Toxicokinetics, Mouse (CD-1)	PO IV IV	50, 500, 2000 mg/kg (range finding) 50, 500, 2000 mg/kg (range finding) 400, 1000, 2000 mg/kg (definitive)	Single dose	[A] 410-FCW-43	No
PNU-141535 Process Impurity Toxicokinetics, Rat (Fischer 344)	IV	500, 1000, 2000 mg/kg	Single dose	(A)410-FCW-43	No
Repeated-Dose Pharmacokinetics/Toxicokinetics					
Gestational Toxicokinetics, Female Mouse (CD-1)	PO	0 (vehicle), 50, 150, 450 mg/kg/day	Daily; Gestation days 6-16	(C)5014-TJF-490A	Yes
7-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	200 mg/kg/day	Twice daily; 7 days	PNU-100766, (D2)1500-5148-JLH-48M	No

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
14-Day Toxicokinetics, Rat (Sprague-Dawley)	IV	0 (vehicle and environmental [saline] controls), 40, 100, 250 mg/kg/day (0, 0, 20, 50, 125 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Range-Finding 14-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 40, 200, 1000 mg/kg/day (0, 20, 100, 500 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
28-Day Toxicokinetics, Rat (Sprague-Dawley)	IV	0 (vehicle), 20, 60, 200 mg/kg/day (0, 10, 30, 100 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes
28-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 20, 50, 125 mg/kg/day (0, 10, 25, 62.5 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes
28-Day Toxicokinetics, Male Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 12.5, 25, 50 and 100 mg/kg	Once daily, 28 days	[A1]1510 5014-TJF-170A	No
53-Day Toxicokinetics, Male Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 100 mg/kg/day	Daily; 53 days	(D)5014-TJF-864	No
90-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 10, 40, 125/80 mg/kg/day (0, 5, 62.5/40 mg/kg/dose)	Twice daily; 3 months Recovery: 1 month	(D)5014-TJF-864	Yes
Segment I and III Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 2.5, 15, 50 mg/kg/day	Males: Daily; 4 weeks prior to and throughout cohabitation until sacrifice F0 Females that Delivered: 2 weeks prior to cohabitation throughout cohabitation, gestation, and postpartum until sacrifice at weaning F0 Supplementary Phase Treated Females: 2 weeks prior to cohabitation until sacrifice on gestation day 13	(C)5014-TJF-490A	Yes
9-Week Fertility Toxicokinetics, Male Rat (Sprague-Dawley)	PO	0 (vehicle), 50, 100 mg/kg/day	Males: daily; 9 weeks Reversibility: up to 12 weeks	(D)5014-TJF-904	Yes
28-Day Toxicokinetics, Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 10, 25, 63 mg/kg/day	Daily; 1 month Recovery: 6 weeks	(D)5014-TJF-864	Yes
7-Week Fertility Toxicokinetics, Male Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 12.5/25, 25/50, 50/100 mg/kg/day (0, 12.5, 25, 50 mg/kg/day on days 1-36 followed by a dose escalation to 0, 25, 50, 100 mg/kg/day, respectively, on days 37-49.	Daily; 7 weeks Reversibility: up to 19 weeks	(D)5014-TJF-864	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
10-Week Fertility Toxicokinetics, Male Rat (Sprague-Dawley)	PO	0 (vehicle), 100 mg/kg/day	Once daily, 10 weeks Reversibility up to 14 weeks	D2-1500-5148-JLH-48	Yes
10-Week Toxicokinetics, Male Rat (Sprague-Dawley)	PO	0 (vehicle), 100 mg/kg/day	Once daily, 10 weeks Testosterone supplemented	D2-1500-5148-JLH-48	No
7-Day Toxicokinetics, Male Rabbit (NZW)	PO	0, 25, 50 and 100 mg/kg/day	Twice daily, 7 days	(A1)1510-5014-TJF-170A-	No
14-Day Toxicokinetics, Dog (Beagle)	IV	0 (vehicle), 30, 60, 120 mg/kg/day (0, 15, 30, 60 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
14-Day Toxicokinetics, Dog (Beagle)	PO	0 (control), 50, 128, 320 mg/kg/day (0, 25, 64, 160 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
1-Month Toxicokinetics, Dog (Beagle)	PO	0 (control), 20, 40, 80 mg/kg/day (0, 10, 20, 40 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(A1)1510-5014-TJF-170A-J255	Yes
1-Month Toxicokinetics, Dog (Beagle)	IV	0 (vehicle), 10, 20, 40 mg/kg/day (0, 5, 10, 20 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(C)5014-TJF-490A	Yes
90-Day Toxicokinetics, Dog (Beagle)	PO	0 (vehicle), 5, 10, 20, 40/30 mg/kg/day (0, 2.5, 5, 10, 20/15 mg/kg/dose)	Twice daily; 3 months Recovery: 2 months	(D)5014-TJF-864	Yes
<b>Distribution</b>					
Caco-2, In VitroTransport	In vitro	NA	NA	PNU-100766 (D)5014-DJH-274A	No
Caco-2/ MDCK, In Vitro Transport	In vitro	NA	NA	[ <sup>14</sup> C]PNU-100766, 30994-JAE-130A	No
Tissue Distribution-Excretion, Male Rat (Sprague-Dawley and Long Evans)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766: (A1)1510-5014-TJF-170A-J255, [ <sup>14</sup> C]PNU-100766: 27983-JPM-40B	No
Tissue Distribution-Excretion, Female Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766: (A1)1510-5014-TJF-170A-J255, [ <sup>14</sup> C]PNU-100766: 37792-EHC-7UA	No
Preliminary Tissue Distribution (WBA), Male Rat (Sprague-Dawley)	PO	250 mg/kg	Single	NS	No
Tissue Distribution/Placental Transfer (WBA), Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV (male) 25 mg/kg PO (pregnant female at 14 day or 18 day gestation)	Single	PNU-100766, (d2)1500-5148-JLH-48M. [ <sup>14</sup> C]PNU-100766, 30994-JAE-130A	Yes

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
<sup>14</sup> C Lacteal Secretion, Female Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766, (D2)1500-5148-JLH-48M [ <sup>14</sup> C]PNU-100766, 30994-JAE-130A	Yes
Plasma Protein Binding, Rat (Sprague-Dawley), Dog (Beagle), Human	In vitro	0.1-100 ug/mL	NA	PNU-100766: (A1)1510-5014-TJF-170A-J255, [ <sup>14</sup> C]PNU 100766: 37792-EHC-7UA	No
<b>Biotransformation</b>					
In Vivo Studies					
<sup>14</sup> C Quantitative Metabolite Profile, Mouse (CD-1)	PO	50, 450 mg/kg	Single	[A1]1510 5014-TJF-170A	No
<sup>14</sup> C Quantitative Metabolite Profile in plasma, Rat (Sprague-Dawley)	PO	25 mg/kg	Single	[A1]1510 5014-TJF-170A	No
<sup>14</sup> C Quantitative Metabolite Profile Biliary Excretion, Rat (Sprague-Dawley)	PO, IV	25 mg/kg PO, 10 mg/kg IV (male and female) Biliary excretion 25 mg/kg PO (males only)	Single	[A1]1510 5014-TJF-170A	No
Preliminary Metabolite Identification, Rat (Sprague-Dawley)	PO	25 mg/kg	Single	PNU-100766: 27774-DAU-71A. [ <sup>14</sup> C]PNU-100766: 27983-JPM-40B; RA 0231.	No
Preliminary Metabolite Identification, Rat (Sprague-Dawley) and Dog (Beagle)	PO	25 mg/kg	Single	NS	No
Quantitative Metabolite Profile, Dog (Beagle)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single	[A1]1510 5014-TJF-170A	No
Preliminary <sup>19</sup> F NMR Excretion, Human	IV	750 mg	Single	see clinical protocol M-1260-0003	No
Preliminary Metabolite Identification, Human	PO, IV and in vitro	Various	Single and multiple	see clinical protocol M-1260-0001-4	No
<sup>14</sup> C and <sup>19</sup> F Quantitative Metabolite Profile/Minor Metabolite Identification, Human	PO	500 mg	Single radiochemical dose given alone or as the morning dose on day 4 of a 10 day bid regimen of unlabelled PNU-100766	[A1]1510 5014-TJF-170A	No

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
In Vitro Studies					
90-Day Enzyme Induction, Rat (Sprague-Dawley)	PO	0 (vehicle), 10, 40, 125/80 mg/kg/day (0, 5, 62.5/40 mg/kg/dose)	Twice daily; 3 months	(D)5014-TJF-864	Yes
Cytochrome P450 Inhibition (Cloned Isoforms), Human	In vitro	10 and 100 uM	NA	NS	No
Preliminary Biotransformation, Rat (Sprague-Dawley)	In vitro	Hepatocyte suspension : 5,000,000 cells/mL, 40 µg/mL (118.6 µM)	1 and 3 hours at 37 °C	NS	No
Preliminary Biotransformation Mechanism-Microsomes-CYP 450 Cloned Isoforms-Liver Slices, Human	In vitro	Various	Various	NS	No
Definitive Biotransformation Mechanism-Chemical oxidation-microsomes-CYP 450 Cloned Isoforms, Human	In vitro	Various	Various	NS	No
Electrochemical Oxidation	NA	Electrochemical anodic oxidation potential of morpholine ring	NA	28596-DMJ-3	No
Preliminary Biotransformation Liver Slices (Rat, Dog, Monkey, Human) and Plasma (Human)	In vitro	Liver slices; 20 mg/mL U-100766; 37°C for 6 or 24 h. Human plasma, 100 ug/mL PNU-100766 37°C for 2 h.	NA	NS	No
Preliminary Monoamine Oxidase Inhibition-Liver S9, Human	In vitro	2, 20, 200 µM	30 minutes	NS	No
Definitive MAO-A Ki-Purified Placental MAO-A, Human	In vitro	0- 500 uM 7-8 Data points	NA	[E] 5014-TJF-967	No
Process Impurity-Stability In Vitro					
PNU-141535 Stability in UDS Incubation Media	In vitro	<u>Experiment 1:</u> 30, 100, 300, 600, 1000, 3000 µg/mL <u>Experiment 2:</u> 30, 60, 200, 600, 2000, 3000 µg/mL	18-20 hour incubation	(A)410-FCW-43	No

**Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid**

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
PNU-141535 Stability In Ames Assay Incubation Medium and Hepatic S9, Rat (Sprague-Dawley)	In vitro	0 (sterile water), 7, 21, 62, 185, 555 µg/plate with metabolic activation 0 (sterile water), 62, 185, 556, 1667, 5000 µg/plate without metabolic activation	2-day incubation	(A)410-FCW-43	No

\* PNU-96403 is a 4-pyridil derivative of oxazolidinone

† 5-day toxicity study in the beagle dog (Study No. 95-903) was summarized in a memo (Kaneko Y. U-100766: 5-Day intravenous toxicity study in two male and two female beagle dogs. Upjohn memo to list, 30 June 1995) and appended to Upjohn Technical Report 1470-95-033.

‡ PNU-105368 is a minor metabolite of PNU-100766

§ PNU-141535 is an impurity of PNU-100766

¶ This radio synthesis was repeated, subsequent lots are denoted by notebook reference "JAE".

**Abbreviations:** CUP =  $\alpha$ -chloralose, urethane, and sodium pentobarbital; DMSO = dimethylsulfoxide; GLP = Good Laboratory Practice; HPLC = high performance liquid chromatography; IP = intraperitoneal; IV = intravenous; LLOQ = lower limit of quantitation; MAO = monoamine oxidase; NA = not applicable; NH = non-heated; NMR = nuclear magnetic resonance spectroscopy; NR = not reported; NS = not specified; NZW = New Zealand White; PO = oral; SD = Sprague-Dawley; THS = terminally heat sterilized; UDS = unscheduled DNA synthesis; WBA = whole body autoradiography